REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks presented herein, is respectfully requested. Claims 1-2 and 6-8 are amended. The pending claims are claims 1-11. No new subject matter has been added. The amendments are made to clarify the claims, and not for reasons relating to patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element may be entitled.

To advance prosecution, claims 1-2 have been amended to no longer recite the phrase "or part thereof." However, it should be made clear that an antigenic molecule of the invention is defined in the specification to be "any molecule wherein that molecule or part thereof is capable of stimulating an immune response" at page 6, lines 33-35. For example, an antigenic molecule of the invention may be a peptide, such as an oligopeptide or polypeptide, or a protein molecule or fragment thereof, e.g., 5-500 amino acids (page 7, lines 20-22). In addition, a "part" of an antigenic molecule may comprise parts which are generated by antigenic-processing machinery within a cell, or generated by other means such as antigenic design or other cell processing means (page 7, lines 23-29).

Claim 6 has been amended to correct grammatical errors.

Claims 7-8 have been amended to recite proper antecedent basis.

This Amendment and Response and the above-referenced SEQUENCE LISTING are filed in part to conform the above-referenced application to the requirements of 37 C.F.R. §§ 1.821 - 1.825. In accordance with 37 C.F.R. § 1.821(e), a copy of the above-submitted SEQUENCE LISTING in ASCII computer readable form is also submitted herewith. The contents of the paper version of the SEQUENCE LISTING and the computer readable form being submitted herewith are the same, and the paper copy of the SEQUENCE LISTING and the computer readable form of the SEQUENCE LISTING do not include new matter.

The 35 U.S.C. §112, Second Paragraph, Indefiniteness Rejection

The Examiner rejected claims 6-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-8, as amended, overcome these rejections. Thus, withdrawal of the 35 U.S.C. § 112(2) rejection is respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Written Description Rejection

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that there is insufficient written description for the phrase "part thereof" of an antigenic molecule. To advance prosecution, the phrase "part thereof" has been deleted from the claims, thus overcoming this rejection.

Withdrawal of the 35 U.S.C. § 112, first paragraph, written description rejection is therefore respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Enablement Rejection

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner alleges that the specification does not reasonably enable the present method (A) having an antigenic molelcule capable of stimulating an immune response (claim 3); (B) wherein the antigenic presentation results in the stimulation of an immune response (claim 11); and (C) wherein the antigenic molecule is a vaccine antigen or vaccine component (claim 4). The Examiner asserts that the use of Applicants' invention as claimed is unpredictable, and that the scope of the claims are not commensurate with the disclosure. Thus, the Examiner alleges it would require an undue amount of experimentation for the art worker to practice the claimed invention. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Applicants' invention is directed to a method of expressing an antigenic molecule on the surface of a cell by introducing a molecule into the cell cytosol by photochemical internalization, wherein the molecule is subsequently presented on the surface of said cell.

As for (A) and (C), above, Applicants disclose that following photochemical internalization (PCI) of the MART-1 peptide, FM3 melanoma cells were susceptible to MART-

1/HLA-A2 cytotoxic T lymphoctyes (CTLs) (Example 2, Figure 3). The MART-1 peptide is recognized in the literature as a molecule capable of stimulating an immune response *in vivo* and *in vitro*, and is known to be used in vaccines. As evidence of this, the Examiner is urged to consider Wang et al., Clinical Cancer Research, 5, 2756 (1999); Philip et al., Journal of Immunotherapy, 23, 168 (2000); and Lee et al., Journal of Immunotherapy, 23, 379 (2000) (a copy of each is enclosed herewith).

Lee et al. report that immunization of mice with a construct directing high-level MART-1 expression elicits a specific, *in vivo* immune response (abstract). In addition, Lee et al. discuss the preparation of a clinical trial involving MART-1 immunization (abstract). Wang et al. describe the immunization of high-risk melanoma patients with the MART-1 minimal peptide, which results in an immune response as measure by ELISA and ELISPOT assays (abstract). Philip et al. demonstrate that expression of a transgene having the MART-1 gene in dendritic cells (DCs) stimulates $CD8^+$ T cells to elicit an immune response (abstract). In addition, MART-1 peptide loaded DCs stimulates T cells elicited an immune response in animals after *in vitro* administration to antigen presenting cells (page 171, left column).

As for (B), above, Applicants disclose that an antigenic molecule is capable of stimulating an immune response (page 6, lines 33-35). Indeed, the Examiner also defines an antigen or antigenic molecule as "a substance that can induce a detectable immune response" (page 3 of the Office Action). Thus, the Examiner is urged to consider that in Example 2, Applicants disclose that the antigenic presentation of MART-1 peptide induces an immune response as evidenced by the CTLs killing the cells expressing the peptide.

Moreover, at page 5, lines 6-14, Applicants disclose that the terms "expressing" and "presenting" refer to the presence of a molecule on the surface of the cell such that at least a portion of the molecule is exposed and accessible to the environment surrounding the cell. Thus, in light of the fact that Applicants disclose cell surface expression, i.e., antigenic presentation, of MART-1 *via* PCI, that MART-1 has been shown to induce an immune response, and is known as a vaccine antigen, it is respectfully requested that Applicants' specification fully enables the claimed invention.

To support the position that Applicants' invention is unpredictable, the Examiner (i) cites to Lynch et al. (Photochem. and Photobio., 49, 453-458 (1989) and Sternberg et al. (U.S. Patent

No. 6,153,639) as evidence that photodynamic therapy (PDT) is also known as PDI, is immunusuppressive, and that PDT can down regulate MHC class I molecules; (ii) cites to Lapes et al. (Journal of Photochemistry and Photobiology B: Biology, 36, 205 (1996)) as evidence that the photosensitizer agent $TPPS_4$ is highly cytotoxic; (iii) cites to Stites et al. (Basic and Clinical Immunology, 6th ed., Appleton and Lange, Norwalk, Connecticut, 693-703 (1987)) as evidence that a claim directed to a method involving a vaccine antigen or vaccine component is unsupported; and (iv) alleges that none of the Examples disclosed in the specification offers substantial support to the claimed invention.

As for (i) and (ii), Lynch et al. discuss that systemic immunosuppression induced by PDT, measured by contact hypersensitivity, is adoptively transferred im mice by B cells and macrophages (abstract). Sternberg et al. relate that PDT has been used to destroy tumor and surrounding tissue (column 1, lines 23-29) and describe photoactive compounds useful in PDT. Sternberg et al.'s compound, B-EA6 was found to have an improved LD_{50} in serum as compared of BPD-MA, a prior art photoactive compound, was found to kill 80% of L1210 cells in an *in vitro* PDT test, and was found to retain the immunodulatory activity of BPD-MA (Examples 4-6). Another compound, A-EA6, was found to decrease expression of MHC I receptors (column 12, lines 15-30). Lapes et al. report a study in which $TPPS_4$ was used in conjunction with PDT to treat patients having metastatic breast cancer (abstract). A side-effect of synthetic $TPPS_4$ is neurotoxicity, but the $TPPS_4$ preparation described by Lapes et al. was found to have negligible neurotoxicity (page 207, right column).

The Examiner is urged to consider that photodynamic therapy (PDT), discussed by Lynch et al., Sternberg et al., and Lapes et al. is a cytotoxic therapy which involves the killing of cells in which the photosensitizer is present by exposing them to light of and appropriate wavelength. See page 1, lines 24-page 4, line 1 of Applicants' specification. In contrast, claims 1-11 are directed towards the use of photochemical internalization (PCI). PCI does not depend upon cell killing (indeed, if the cells are killed then the method is ineffective), but PCI can be used, for example, as a method for introducing molecules, e.g., membrane impermeable molecules, into the cytosol of a cell which does not result in cell death (page 4, lines 2-21 of Applicants' specification). Thus, PCI is distinct from PDT.

In addition, the Examiner is also urged to consider that there are reports in the literature

that PDT can stimulate immunological responses. As evidence of this, the Examiner is respectfully requested to consider Canti et al., Anti-Cancer Drugs, 5, 443 (1994); Korbelik and Dougherty, Cancer Research, 59, 1941 (1999); and de Vree et al., Cancer Research, 56, 2980 (1996) (a copy of each is enclosed herewith). In fact, it is believed that the stimulating effects on the immune system in many cases is an important part of the mechanism behind the clinical effects of PDT. Moreover, Applicants disclose that the overall effect of PCI is a stimulation of antigenic presentation (Example 2). Even if the PCI procedure may down regulate MHC Class I, as the Examiner asserts Sternberg et al. teach, the results of Example 2 show that this effect is more than counterbalanced by the positive effects on antigenic presentation by PCI. Furthermore, Applicants disclose that cytotoxicity can be limited to an appropriately low level by selecting an appropriate light dose in relation to the concentration of the photosensitizing agent (page 15, lines 19-23).

As for (iii), above, the Stites et al. document is a "Glossary of Terms Commonly Used in Immunology", wherein vaccination is defined as "immunization with antigens administered for the prevention of infectious diseases" (page 703). Applicants disclose that surface expression of an antigenic molecule or vaccine component can be achieved using the methods of the invention. See, for example, Example 2 which discloses the cell surface expression of the MART-1 peptide, which, as argued above, is a known vaccine component. Once an antigenic molecule, such as the MART-1 peptide, is presented on the surface of a cell, Applicants submit that there is no reason that proven antigenic or vaccine peptides would not stimulate an immune response and/or elicit a protective effect. The Examiner has not provided any evidence that this would not be the case. For peptides that are not yet proven to be antigenic or capable of stimulating a protective effect, routine methods could be used to determine if these expressed peptides are antigenic and/or protective.

Regarding (iv), above, the Examiner alleges that Example 2 does not contain a control, and thus results can not be interpreted. However, it is Applicants' position that the relevant controls are disclosed in Example 2, e.g., Figure 3 clearly discloses the result of an experiment where cells were not exposed to light. In addition, for each light dose, Applicants measured the spontaneous ^{51}Cr release, i.e., the ^{51}Cr released from cells treated with the MART-1 peptide, photosensitizer, and light, but where cytotoxic T-cells were not added (page 21, lines 28-36).

The increased ^{51}Cr release disclosed in Figure 3 is a result of increased presentation of antigen induced by the light treatment, and is not an unspecific direct effect of the photochemical treatment on ^{51}Cr release. The fact that light-induced increases in ^{51}Cr-release are observed even when corrected for spontaneous ^{51}Cr-release at different light doses shows that light treatment alone is not responsible for the observed increases in ^{51}Cr-release. This must be due to the positive effects of PCI on antigen presentation, since the ^{51}Cr-release is dependent upon the presence of specific T-cells. Since this is true with the photosensitizer (which is known to induce biological effects in the cells upon illumination), it is highly unlikely that a similar experiment without the sensitizer should give a different conclusion, since a mere light treatment generally does not induce biological effects in the illuminated cells. Thus, the appropriate controls are disclosed in Example 2, and substantial support is disclosed for the claimed invention.

The Examiner alleges that Example 3 "teaches away" from the claimed invention. Example 3 discloses high levels of internalization of an antigenic molecule, specifically, HRP, immediately following light exposure. In addition, Example 3 discloses initial relocalization of the HRP antigenic molecule to the cytosol of the cell, i.e., the first step in antigenic presentation of the molecule. These conditions do not allow sufficient time for the cells to present the antigen on the cell surface. As a comparison, in Example 2, cell surface presentation of an antigenic molecule, specifically, MART-1, is disclosed after exposure of the cells to light and incubation for eighteen hours, an amount of time sufficient for the antigenic molecule to move from the cytosol to the surface of the cell. Hence, Example 3 supports the claimed invention.

Regarding Figure 4, the Examiner's attention is directed to that fact that the paragraph on page 16, lines 27-34 has been amended to correct a typographical error. Given that Example 3 discloses the initial step wherein HRP is contacting with the external surface of the cell and is internalized into the cytosol (page 22, line 10), it is clear that the amount of HRP in intact cells should be distributed between the cytosol and the cytosol-free cell corpses. Thus, Example 4 is relevant to the claimed invention.

Furthermore, the scope of enablement provided by the present specification need only bear a "reasonable correlation" to the scope of the claims. In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). It is well-settled that there is no requirement for working examples to fulfill the requirements of 35 U.S.C. §112, first paragraph, if the invention is otherwise disclosed so that

one of ordinary skill in the art can practice the invention without undue experimentation. In re Robins, 429 F.2d 452, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970); In re Borokowski et al., 422 F.2d 904, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970).

Satisfaction of the enablement requirement of § 112 is not precluded by the necessity for a considerable amount of experimentation, if it is merely routine. Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982). "The key word is 'undue' not 'experimentation.'" In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Moreover, the fact that the outcome of such a synthesis/screening program is unpredictable is precisely why a screening program is carried out. The Examiner simply cannot reasonably contend that a screening program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate bioactive molecules do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Thus, the fact that an antigenic molecule, e.g., a vaccine antigen or vaccine component, would have to be screened in order to determine if the molecule elicited an antigenic and/or protective response is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

Thus, given the above, the Examiner is respectfully requested to consider the claimed methods are not unpredictable and Applicants' specification fully enables the claimed invention. It is respectfully submitted that the pending claims are in conformance with § 112(1). Hence, withdrawal of the § 112(1) enablement rejection is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-371-2106) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 24 day of October, 2001.

Candis B. Buending
Name

Signature